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Antilymphocytic antibodies and marrow transplantation. XII. Suppression of graft-versus-host disease by T-cell-modulating and depleting antimouse CD3 antibody is most effective when preinjected in the marrow recipient.

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A hamster antimouse CD3 monoclonal antibody (MoAb) opened the way to experimental studies on the suppression of allograft rejection and cytokine-related morbidity after treatment with antibodies modulating the CD3/T-cell receptor complex (CD3/TCR). Because earlier attempts to suppress graft-versus-host disease (GVHD) in patients by in vitro treatment of donor marrow with anti-CD3 MoAb had remained inconclusive, we used a rat IgG2b antimouse CD3 MoAb (17A2) with fewer side effects to analyze suppression of GVHD in the mouse model. Detailed phenotyping of blood, spleen, and lymphnode T cells after the injection of 400 micrograms 17A2 in C57BL/6 mice showed 60% CD3 downmodulation and 50% T-cell depletion for spleen cells. Injection of these spleen cells, together with bone marrow cells, in fully mismatched preirradiated CBA mice delayed GVHD by only 6 days. Ex vivo treatment of donor cells with 17A2 was not effective. In contrast, conditioning of marrow recipients with a single injection of 17A2 delayed 50% GVHD mortality by 100 days and prevented GVHD altogether after prolonged treatment, with survivors showing complete chimerism and specific transplantation tolerance. This difference in antibody effect contrasts with earlier experiences with nonmodulating but more strongly T-cell-depleting MoAbs of the same isotype, which prevent GVHD no matter whether applied in vitro or injected into donor or recipient mice. Our data indicate that CD3/TCR reexpression in marrow recipients with no circulating 17A2 is the reason why ex vivo donor cell treatment with anti-CD3 MoAb is comparatively ineffective. Our data, which allow separate evaluation of cell-depleting and cell-modulating antibody activity, help to explain previous clinical failure to suppress GVHD and provide evidence in favor of conditioning the marrow recipient with anti-CD3 MoAb as a therapeutic alternative.

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